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Intrathecal Serotherapy of Tetanus

I. Explanation of complications
II. Comparison of intrathecal Tetanus Immune Globulin and Tetanus Antitoxin

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Opinions differ as to the necessity of the usage, dosage and the site of administration of antitoxin. From animal experiments[1-4] and clinical studies[5-8] it has been shown that the administration of antitoxin greatly reduces the mortality rate. Although some investigators claimed that there is no beneficial effect of antitoxin administration[9-10] this type of treatment has been used by most authorities since 1894.[11-13]

The first successful intrathecal T. A. T. (equine tetanus antitoxin) administration was done by Leyden in 1901.[14] In animal experiments, the intrathecal administration of T. A. T. gave a better result than intramuscular and intravenous injections.[1-2] Therefore, this type of treatment was used successfully in many countries until 1940-1945.[15-37] At that time there was a strong opposition of the opinion that most of the complications during this type of treatment were due to intrathecal administration of T. A. T. rather than the disease itself.[38-39] In 1945, Pratt[40] suggested that intrathecal administration of T. A. T. should be stopped until a new T. A. T. with no side effects was developed. Then intrathecal serotherapy was abandoned until 1967 when we started again and obtained very satisfactory results.[41] After this preliminary report[41], a double-blind study on pure bred dogs (beagles) gave statistically significant better results with intracisternal treatment of T. A. T. and prednisolone mixture.[4] In clinical application, 28 cases of neonatal tetanus and three cases of tetanus in young children were also treated with T. A. T. and prednisolone mixture by the lumber intrathecal route. Only three neonates died; the others recovered in 15.6 days (average). The case fatality rate for neonates was 10.7 %. All three young children survived. On follow-up, growth and development were normal.[4]

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This study was done in two sections:

I. Animal experiments: Since intrathecal treatment had been criticized due to its severe side effects,[38-40] animal experiments were planned in order to find a reasonable answer to the cause of complications.

II. Clinical study: This study was planned in order to find an answer to the question, "Is it possible to get a better result with intrathecal T. I. G. (tetanus immune globulin human) than intrathecal T. A. T. in the treatment of neonatal tetanus?".

I. ANIMAL EXPERIMENTS

Materials and Methods

56 mongrel dogs weighing between 7 to 11 kg. were used in this study. The animals were randomly divided into 7 groups, 8 (dogs) in each group. Different materials were injected by the cysternal route after the same amount of cerebral spinal fluid (CSF) had been with drawn and observed to be clear. All the animals were observed for 3 days after this procedure (Table I.).

Group I. Received 5 ml. of T. A. T. (Wyeth) (1 ml containing 2300 U. of antitoxin, 0.25 % phenol and 1/20,000 thimerosal as preservative).

Group II. Received 5 ml T. A. T. (1 ml. containing 2300 U. of antitoxin without any preservative) obtained by dialization of T. A. T. (Wyeth).

Group III. Were injected with 1 ml. T. I. G. (Cutter) (1 ml. containing 250 U. of antitoxin and 0.01 % thimerosal).

Group IV. Received 5 ml. normal saline that contained 0.25 % phenol.

Group V. Were given 10 ml. normal saline that contained 0.5 % phenol.

Group VI. Received 5 ml. normal saline that contained 0.01 % thimerosal.

Group VII. Were injected with 5 ml. normal saline,

Results

After the injection of commercial T. A. T. preparation which contained phenol as preservative (Group I) and N. saline with phenol (Groups IV and V) all the dogs had severe tonic-clonic seizures of face and ear muscles starting from the time of injection and lasting for 30 minutes.

TABLE I

REACTIONS OF DOGS TO INTRACISTERNAL T.A.T., T.I.G AND OTHER SOLUTIONS

Group	Number of Dogs	Intracisternal Injection	Units/ml	Volume	Preservative	Reactions
I.	8	T. A. T.	2300	5 ml	0.25 % Phenol and 1/20,000 thimerosal	Convulsion
II.	8	T. A. T. (dialized)	2300	5 ml	None	None
III.	8	T. I. G. For I. M. application	250	1 ml	1/10,000 Thimerosal	Ataxic gait
IV.	8	9.9 % Saline with Phenol	None	5 ml	0.25 % Phenol	Convulsions
V.	8	0.9 % Saline with Phenol	None	10 ml	0.5 % Phenol	Convulsions (5 dogs died)
VI.	8	0.9 % Saline with Thimerasol	None	5 ml	1/10,000 Thimerosal	None
VII.	8	0.9 % Saline	None	5 ml	None	None

They also showed shaking movements of the head for about 12 hours and they continuously had salivation and scratched the ground. Five dogs in Group V died within 7-15 minutes with convulsions and apena.

In Group II, dogs were injected intracysternally with T. A. T. preparation which was dialized to free it from preservatives. This group didn't demonstrate any side reaction. The control group (Group VII) which received N. saline injection without any preservative also had no reactions.

Group III, were injected with 1 ml. 250 U. T. I. G. Except for ataxic gait which was observed for about 12 hours, no severe reactions were observed.

Group VI, which was given N. saline with 1/10,000 thimerosal showed no adverse reaction.

Discussion

It was hypothesized that phenol or other preservatives used in homologous or heterologous antitetanus serum were irritants and could be responsible for some additional complications of intrathecal treatment. It was evident from this study that phenol, in concentrations used for preservation of biological products did produce convulsions (Group IV), but thimerosal didn't produce any side effects at the concentration of 1/10,000 (Group VI).

Intrathecal administration of phenol and thimerosal free T. A. T. did not produce convulsions in any of eight dogs (Group II).

While 0.25 % phenol in N. saline produce convulsions, (Group IV) when the volume and concentration of phenol in saline solutions was doubled, 5 dogs out of 8 died after severe convulsions and apnea (Group V).

After this experimental study we can say that the side reactions to antitetanus serum are due to phenol product but not to antitoxin itself.

In conclusion, antitoxin preparations for intrathecal use should neither contain high concentrations of preservatives nor their chemical compositions, as these may be hazardous to the CNS tissues.

II. CLINICAL STUDY

Material and Method

110 neonatal tetanus cases were admitted to the hospital from September, 1970 to January, 1975. The patients were randomly given either intrathecally 250 U. of T. I. G. or intrathecally 2500 U. of T, A. T. Other methods of treatment were the same in both groups. as indicated below.

As soon as a case was diagnosed 2-4 mg. diazepam was given intravenously for sedation. This application was found to be helpful and necessary for intrathecal injection. All intrathecal injections were given through lumbar puncture. The patients'umblicus were cleaned with hydrogen peroxide. 2500 U. of T. A. T. were given through intramuscular and intravenous routes, respectively. T. I. G. or T. A. T. were mixed with 12.5 mg. prednisolone and warmed to room temperature and then injected intrathecally within 5 minutes. Before the intrathecal injection, the same amount of CSF was withdrawn. All cases were given 10 mg. prednisolone in two divided doses orally. Sedation was continued with oral diazepam 2-4 mg. every two hours (maximum 15 mg./kg. daily), for severe convulsion medication was injected intravenously. If the convulsion continued, as in rare instances, phenobartibal (15 mg./kg. daily) was added. For the prevention of super infections, crystalline penicillin 400,000 U. and kanamycin 15 mg./kg. was given intramuscularly. A private room was provided for tetanus patients to stay with their mothers. All the patients were fed by a naso-gastric tube and none of them had tracheotomy. Intravenous fluids were given to only severely dehydrated cases.

Since T. I. G. and T. A. T. differed in color and volume, the doubleblind method could not be used in the study.

Results

Six cases from the T. I. G. group and one case from the T. A. T. group were excluded from the study because their parents did not let their children stay in the hospital until the treatment was completed. Table II shows the various characteristics of the two groups.

TABLE II

COMPARISON OF VARIOUS CHARACTERISTICS OF TWO GROUPS

Characteristics Number of cases	Intrathecal T. I. G. 49	Intrathecal T.A.T. 54
Number of deaths	10 (20.5 %)	8 (14.8 %)
Sex:		
Female	13 (26.5 %)	15 (27.7 %)
Male	36 (73.5 %)	39 (72.3 %)
Weight (Mean ± 2 SD)	3017 ± 1.64	3028 ± 1.59
Age (Days)	8.1 ± 1.35	8.3 ± 1.42
Incubation Period (Days)	6.5 ± 1.85	6.9 ± 1.88
Days of Hospitilization (survivors)	15.2 ± 3.20	15.9 ± 3.40
Days to death	5.2 ± 2.68	4.7 ± 2.45
Days of Sedation (survivors)	9.1 ± 1.93	8.7 ± 1.82
Days of Gavge	7.8 ± 2.15	7.6 ± 2.65

Ten cases out 49 from the T. I. G. group (20.5 %) and 8 cases out of 54 in the T. A. T. group (14.8 %) died. The difference of case fatality rate was not statistically significant in the two groups, ($X^2 = 0.53$; 0.5 p 0.30).

In both groups, the case fatality rate was higher in cases with less than 7 days incubation .In the T. I. G. group there were 32 cases with less than 7 days incubation, of whom 9 died (28.1 %). In the T. A. T. group from 29 cases with less than 7 days incubation, there were 7 deaths (24.1 %). There was one death in each group whose incubation period was 7 days or more.

Regarding the duration of hospitalization and the duration of sedation there were no significant differences between the two groups. However, regardless of the type of antitoxin used, the length of incubation was found to influence the case fatality rate significantly ($X^2 = 7.54$; $p < 0.01$).

Comments

The animal experiments which were mentioned in the first part of this study showed that, if there is not an excessive amount of phenol in the preparations, T. A. T. and T. I. G. can be given by the intrathecal route.

In the second part of this study, intrathecal T. I. G. and T. A. T. treatments were compared. On the basis of case fatility ratio, length of hospitalization, days of sedation, and the amount of sedatioı, there was no significant difference between 2500 units of T. A. T. and 250 units of T. I. G. in the treatment of neonatal tetanus.

In almost all of the developing countries there are no T. I. G. preparations. If both preparations were available, T. I. G. would be preferrable.

Tetanus is a problem of developing countries; for each death from tetanus in a developed country, there are approximately 135 deaths in developing countries.[42] The number of deaths from tetanus per year in the world is more than 420,000.[42] Preventive measures, especially vaccination, is essential for the eradication of tetanus. As tetanus most frequently occurs in poorer countries, where laboratories and intensive care units are limited, the treatment of tetanus must be cheap and simple.

Summary

1. Animal experiments: All the dogs had severe tonicclonic seizures after the intracysternal injection of T. A. T. and 0.9 % saline with phenol. Intracysternal injection of phenol free T. A. T. and T. I. G. did not produce complications.

2. Clinical Study: 49 infants with tetanus neonatorum were treated with intrathecal 250 units of T. I. G. and prednisolone mixture (case fatality rate, 20.5 %). 54 cases were treated with intrathecal 2500 units of T. A. T. and prednisolone mixture (case fatality rate 14.8 %). Other methods of treatment were the same in both groups. There were no significant differences in the treatment groups.

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